REMARKS

The Office Action dated May 11, 2010 has been reviewed and the comments of the U.S. Patent and Trademark Office ("Office") have been considered. The following remarks are respectfully submitted to place the application in condition for allowance.

1. Summary of Claims

Claims 5 and 11 are pending, and claims 1-4 and 6-10 were cancelled previously. Claim 5 has been amended. No new matter has been introduced by the amendments to the claims. Accordingly, Applicants respectfully request entry of the amended claims.

2. Claim Rejection under 35 USC § 103

The Office rejected claims 5 and 11 under 35 USC § 103(a) as allegedly being obvious over Stein *et al.*, (*Journal of Medical Virology*, 1994)("Stein"), in view of Bacheler *et al.* (*Journal of Virology,* 2001)("Bacheler") as evidenced by Servais *et al.*, (GenBank Accession Number CAB86592, GI:7529531; 2001) ("Servais").

The Office asserted that Stein discloses the steps receiving a sample from an HIV-infected patient, determining whether the sample comprises a nucleic acid encoding HIV reverse transcriptase with a mutation at position 194 from wild type amino acid glutamate, and correlating the presence of the mutation to a change in effectiveness or susceptibility of the nucleoside reverse transcriptase inhibitor azidothymidine (AZT). (Office Action at page 4). Due to Stein's failure to disclose the specific mutation E194G, the Office cited Servais as evidence of the E194G mutation in the reverse transcriptase in samples from patients who had been treated with a first anti-HIV therapy with the reverse transcription inhibitors zidovudine and zalcitabine. (*Id.*) The Office acknowledged that Stein does not teach introducing a RTI for a second therapy to a pre-treated patient sample containing the E194G mutation, and cited Bacheler as allegedly disclosing introducing the reverse transcription inhibitors Efavirenz, Nevirapine or Delavirdine in a second therapy. The Office further alleged that Bacheler teach steps similar to the current invention of determining the susceptibility of HIV having a reverse transcriptase mutation to the HIV reverse transcriptase inhibitor in the sample; (v) comparing the anti-HIV drug effectiveness in the sample with a wild type HIV HXB2, (vi) correlating the

presence of the reverse transcriptase mutation to a change in the susceptibility of the HIV reverse transcriptase inhibitor, (vii) determining whether said sample comprises an HIV reverse transcriptase mutation at the position 41, 67, 70, 74, 98, 100, 101, 103, 106, 108, 181, 184, 188, 190, 210, 215, 225, or 227; and analyzing drug susceptibility as in steps (viii) – (x) of the current invention. (*Id.* at page 5). The Office concluded that it would have been obvious to one of skill in the art at the time of the invention to combine the teaching of Stein, Servais and Bacheler to modify the method of Stein and add the steps of Bacheler for evaluating a second reverse transcriptase therapy. (*Id.* at page 6).

Applicants disagree that the claimed invention is obvious in view of the cited art. In contrast to the references, claim 5 as currently amended is directed to a method for evaluating a change in susceptibility of HIV to a reverse transcriptase inhibitor for a second anti-HIV therapy comprising: (i) receiving a sample from an HIV-infected patient who has been treated with a first anti-HIV therapy; ii) determining whether said sample from said HIV-infected patient comprises an HIV reverse transcriptase having a mutation at the position 194, wherein the wild type amino acid glutamate is mutated to glycine (E194G) as compared to the wild-type HIV strain IIIB/LAI; (iii) introducing a reverse transcriptase inhibitor selected from Abacavir, Capravirine, Lamivudine, Didanosine, Stavudine, Adefovir, DPC-086, DPC-083, Tenofovir, and compound 1 (Benzonitrile, 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidiny-l]oxy]-3,5-dimethyl-, compound 1) for said second anti-HIV therapy to said sample from said HIV-infected patient containing said mutation; (iv) determining the susceptibility of said HIV having said reverse transcriptase mutation of step (ii) to said HIV reverse transcriptase inhibitor in said sample; (v) comparing the anti-HIV drug effectiveness in said sample containing said reverse transcriptase mutation with a sample not containing such said mutation; and (vi) correlating the presence of said reverse transcriptase mutation of step (ii) to a change in the susceptibility of said HIV reverse transcriptase inhibitor.

Moreover, claim 11 is directed to the method of claim 5 further comprising: (vii) determining whether said sample from said HIV-infected patient comprises an HIV reverse transcriptase having a mutation E194G compared to the wild-type HIV strain IIIB/LAI, and at least one additional mutation in the HIV reverse transcriptase of the wild-type HIV strain IIIB/LAI at the position selected from 41, 62, 65, 67, 69, 70, 74, 75, 98, 100, 101, 103, 106, 108, 116, 118, 138, 151, 178, 181, 184, 188, 190, 210, 215, 219, 225, 227, 230, 234, 236, and 238;

(viii) determining the susceptibility of said HIV having said reverse transcriptase mutations of step (vii) to said HIV reverse transcriptase inhibitor in said sample; (ix) comparing the anti-HIV drug effectiveness in said sample containing said reverse transcriptase mutations with a sample not containing such said mutations ; and (x) correlating the presence of said reverse transcriptase mutations of step (vii) to a change in the susceptibility of said HIV reverse transcriptase inhibitor.

As noted by the Office, Stein does not teach determining whether a sample from an HIV infected patient comprises a HIV reverse transcriptase with the mutation E194G, or introducing a reverse transcriptase inhibitor as a second therapy to the sample from the pre-treated patient. In citing Servais as identifying the mutation E194G, the Office noted that the mutation was evidenced after treatment only with zidovudine and zalcitabine. There is no indication in the cited art that the same E194G mutation would be identified in treatment with AZT, as tested by Stein, or any other RTI. Furthermore, Stein and Servais do not teach identifying a mutation E194G in combination with any other mutation.

Bacheler teach HIV susceptibility to combination drug therapy. Bacheler, however, does not teach a HIV RT mutation at position 194, either after the first therapy or after a second therapy with a reverse transcriptase inhibitor. Bacheler also does not teach introducing a reverse transcriptase inhibitor selected from Abacavir, Capravirine, Lamivudine, Didanosine, Stavudine, Adefovir, DPC-086, DPC-083, Tenofovir, and compound 1 (Benzonitrile, 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidiny-l]oxy]-3,5-dimethyl-, compound 1) for said second anti-HIV therapy. As with Stein, Bacheler also does not teach identifying a mutation E194G in combination with any other mutation.

Furthermore, there is no suggestion in cited references to give one of skill in the art reason to identify a mutation E194G in combination with any other mutation and correlate the presence of the reverse transcriptase mutation to a change in the susceptibility of a HIV reverse transcriptase inhibitor. Although the cited references may have determined whether a HIV RT mutation is present using single or combination drug therapy, that is not the same as determining whether a specific mutation, such as E194G in the current invention, is present with at least one additional mutation in the HIV RT, such as a position selected from 41, 62, 65, 67, 69, 70, 74, 75, 98, 100, 101, 103, 106, 108, 116, 118, 138, 151, 178, 181, 184, 188, 190, 210, 215, 219, 225, 227, 230, 234, 236, and 238 in the current invention. Determining specific combinations of

mutations is not the same process as identifying multiple mutations in a sample. The Office appears to have incorrectly compared the teaching in Bacheler for determining whether the sample comprises a HIV reverse transcriptase mutation at position 41, 67, 70, 74, 98, 100, 101, 103, 106, 108, 181, 184, 188, 190, 210, 215, 225, or 227 with the requirement in the current invention for a combination or those mutations with E194G. The current invention requires determining the combination of those specific mutations with E194G, determining the susceptibility of HIV having those combinations of reverse transcriptase mutations to HIV reverse transcriptase inhibitors, comparing the anti-HIV drug effectiveness containing those reverse transcriptase mutations with a sample not containing such said mutations; and correlating the presence of those reverse transcriptase mutations to a change in the susceptibility of the HIV reverse transcriptase inhibitor. These steps are not taught or suggested by the cited references Stein, Bacheler and Servais.

In light of the claim amendments and comments above that Stein in view of Bacheler and Servais do not teach all of the elements of the claimed invention, one of skill in the art would have no reason to combine the references to perform the claimed method for evaluating a change in susceptibility of HIV to a reverse transcriptase inhibitor. The skilled artisan would have no reasonable expectation of success to perform the method that uses multiple HIV reverse transcriptase inhibitor therapy, particularly identifying the specific combinations of RT mutations, and correlating the presence of reverse transcriptase mutation(s) to a change in the susceptibility of the HIV reverse transcriptase inhibitor. Thus, Applicants respectfully request withdrawal of the rejection of claims 5 and 11 under 35 U.S.C. § 103(a)

3. Conclusion

In view of the above amendment, Applicants believe the pending application is in condition for allowance and requests favorable action on the merits. Should the Examiner feel that any issues remain, Applicants request that the Examiner contact the undersigned so that the issues may be expeditiously addressed and prosecution of the instant application continue.

Applicants submit concurrently a request for a three-month extension of time under 37 C.F.R. § 1.136 and a request for continued examination under 37 C.F.R. § 1.114 with the accompanying fees set forth in 37 C.F.R. §§ 1.17(a)(1) and (e) paid by credit card in the amount of $940.00. In the event that any extension of time is necessary to prevent the abandonment of this patent application, then such extension of time is petitioned. The U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, from which the undersigned is authorized to draw, under Order No. 026038.0248PTUS.

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Respectfully submitted,

By _____

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